Associations of Perinatal Clinical and Magnetic Resonance Imaging Measures with Developmental Outcomes in Children Born Very Preterm

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Objective To identify perinatal risk factors associated with long-term neurocognitive and behavioral impairments in children born very preterm using a multivariate, partial least squares approach.

Study design Twenty-seven perinatal clinical and magnetic resonance imaging measures were collected at birth and during the neonatal intensive care stay for 105 neonates born very preterm (≤32 weeks gestational age). One-half of the children returned for neuropsychological assessments at 2 and 4 years of age. Parent-reported behavioral measures were also obtained at 4 years of age. Three partial least squares analyses were performed to determine associations between clinical and radiologic measures with cognitive outcomes at 2 and 4 years of age, as well as with behavioral measures at 4 years of age.

Results Within the first components of each analysis, only intrauterine growth restriction, male sex, and absence of antenatal corticosteroid use were associated with poorer cognitive and language ability at 2 and 4 years of age, accounting for 79.6% and 71.4% of the total variance, respectively. In addition, white matter injury at term-equivalent age contributed to more problematic internalizing behaviors, behavioral symptoms, and impaired executive function at 4 years of age, accounting for 67.9% of the total variance.

Conclusions Using this data-driven multivariate approach, specific measures in prenatal and early postnatal life are shown to be selectively and significantly associated with cognitive and behavioral outcomes in children born very preterm. Early detection of risk factors can help inform prognoses of children at greatest risk of long-term impairments. *(J Pediatr 2016;170:90-6)*.

Children born less than 32 weeks gestation are immediately at a disadvantage. Between 20% and 50% of these children develop cognitive and language difficulties, 8% develop cerebral palsy, and 40% develop motor deficits as early as 1 year of age.[1,2] Through later childhood, adolescence, and adulthood, impairments extend to attention, social, and emotional difficulties, as well as to executive dysfunction, such as impaired working memory, inhibition, and planning skills.[3-5] Thus, prediction of compromised long-term outcomes is important in identifying developmental prognoses of very preterm–born children as early as possible.

The precise mechanisms of prematurity are not well understood and involve circumstances such as infection, premature rupture of membranes, and multiple births, among others.[6] Previous studies that have attempted to determine early predictive models have identified a combination of factors associated with adverse outcomes. A multisite study reported that exposure to antenatal corticosteroids, female sex, singleton birth, and higher birth weight were associated with reduced risk of death and gross neurodevelopmental impairment.[7] Fetal growth restriction is reportedly associated with comprised cognitive, language, and memory ability in children born very preterm.[8] Furthermore, abnormalities detected on magnetic resonance imaging (MRI), such as white matter injury, ventriculomegaly, and intraventricular hemorrhage (IVH), are common in infants born preterm and are linked to impaired later neurodevelopmental outcomes.[9] Executive function in later childhood, however, has been associated with early postnatal growth, but not with neonatal complications.[10]

Sophisticated multivariate analyses, such as partial least squares (PLS), are needed to disentangle complex clinical profiles children born very preterm experience at birth. Advantages of this approach include more accurate predictions than those provided by multiple regression–derived models, more stability in handling co-related variables, and simultaneous models for multiple dependent measures.[11] In the present longitudinal study of children born very preterm, we used a PLS approach to identify which combinations of clinical and radiologic characteristics are most predictive of compromised neurodevelopment in later childhood.

GMH	Germinal matrix hemorrhage
IUGR	Intrauterine growth restriction
IVH	Intraventricular hemorrhage
MRI	Magnetic resonance imaging
PLS	Partial least squares
PVHI	Periventricular venous hemorrhagic infarction

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Methods

A total of 105 very preterm neonates (median gestational age at birth, 28.6 weeks; range, 24.4-32.9 weeks) were recruited for this longitudinal research study from the neonatal intensive care unit at The Hospital for Sick Children between 2008 and 2010. Neonates with a known chromosomal or major congenital abnormality were excluded from recruitment. Parents of each neonate provided signed informed consent for participation in the study, access to medical records, and follow-up participation. This research study was approved by The Hospital for Sick Children's Research Ethics Board.

From the original cohort, 5 neonates died in infancy. At 2 years of age, 52 children returned for developmental assessments and at 4 years of age, 53 children returned for neuropsychological and behavioral assessments. Forty-one children (77%) from the 2 groups were followed longitudinally at both 2 and 4 years of age.

Perinatal Clinical Measures

Perinatal clinical data for each neonate were obtained by the medical staff and clinicians, including gestational age, birth weight, head circumference, sex, and delivery type (cesarean or vaginal). Significant events during pregnancy were also recorded, such as whether the mother experienced premature rupture of membranes and whether she was given antenatal corticosteroids to aid the baby's lung development. Intrauterine growth restriction (IUGR), a significant reduction in fetal growth rate, was noted as well. Immediately after birth, measures of illness included Apgar scores at 1 and 5 minutes, the Clinical Risk Index for Babies II, patent ductus arteriosus, necrotizing enterocolitis, and sepsis (defined as a positive blood or cerebrospinal fluid culture and antibiotic therapy for longer than 5 days). In addition, data on medical treatments were collected for each neonate, including the number of days on positive pressure ventilation, endotracheal tube, continuous positive airway pressure, supplemental oxygen, and total parenteral nutrition. On admission to the neonatal intensive care unit, all infants were started on an amino acid infusion.

Radiologic Measures

Within 2 weeks of birth and at term-equivalent age, each neonate underwent MRI as part of the research study. Pediatric neuroradiologists and neurologists assessed the structural T1- and T2-weighted neuroanatomic images for the presence of radiologic findings. From the initial MRI scan acquired within 2 weeks of birth, white matter injury was graded on a scale of 1-3, representing no injury, mild to moderate injury (T1 signal abnormalities in 3 or fewer areas), and severe injury (T1 signal abnormalities in >5% of a hemisphere).[12] The presence and grades of germinal matrix hemorrhage (GMH)/IVH, on a scale of 0 (no hemorrhage) to 4 (periventricular venous hemorrhagic infarction [PVHI] associated with IVH), corresponding to levels of bleeding within the germinal matrix of the brain, were determined as well. This was based on the Papile scale (GMH 1-4) for computed tomography findings[13] and on the Volpe scale for cranial ultrasonography findings adapted to MRI findings (IVH1-3, PVHI).[14] In the present study, GMH1/IVH1 is defined as hemorrhage limited to the germinal matrix, GMH2/IVH2 includes an intraventricular hemorrhagic component, GMH3/IVH3 also includes ventriculomegaly, and GMH4/PVHI is characterized by PVHI associated with IVH.[15] From the second MRI acquired at term-equivalent age, the presence of persistent white matter injury and remaining indications of hemorrhage were noted.

Developmental Assessments

Follow-up developmental assessments were performed for 52 children at 2 years of age to assess overall cognitive, language, and motor ability using the Bayley Scales of Infant and Toddler Development, Third Edition.[16] At 4 years of age, 53 children returned and underwent neuropsychological assessments. IQ was measured using the Wechsler Preschool and Primary Scales of Intelligence, Third Edition[17] using Canadian norms. Three different indices of cognitive ability were obtained: verbal IQ, performance IQ, and full-scale IQ. Overall language ability measuring receptive and expressive language, yielding a core language summary score, was determined by the Clinical Evaluation of Language Fundamentals–Preschool, Second Edition.[18] Visuomotor integration ability and supplemental tests of visual perception and motor coordination were assessed using the Beery-Buktenica Test of Visual Motor Integration.[19] For each assessment, raw scores were converted into standardized scores with a population mean of 100 (50th percentile of typical development) and SD of 15.

Behavioral Measures

Parent-reported questionnaires of each child's behavioral functioning were obtained at 4 years of age. Standardized T-scores were calculated for each questionnaire with a population mean of 50 and SD of 10. A summary T-score of executive functioning was determined from the Behavioral Rating Inventory of Executive Functioning–Preschool,[20] which assesses self-regulatory skills, such as planning, flexibility, information generation, impulse inhibition, and working memory.

Behavior and emotional functioning were assessed through parent responses on the Behavior Assessment System for Children Parent Rating Scales.[21] This questionnaire yields 4 composite T-scores: externalizing problems, internalizing problems, behavioral symptoms index, and adaptive skills. The externalizing problems index includes information of hyperactivity and aggression, and the internalizing problems index includes information of anxiety, depression, and somatization. The behavioral symptoms index covers constructs related to atypicality, withdrawal, and attention problems, and the adaptive skills index covers constructs related to adaptability, social skills, activities of daily living, and functional communication.